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☐	L1	pharmacokinetics same model same predict$	173

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☐ 1. Document ID: US 20020010550 A1

L2: Entry 1 of 2 File: PGPB Jan 24, 2002

PGPUB-DOCUMENT-NUMBER: 20020010550
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020010550 A1

TITLE: PHARMACOKINETIC-BASED DRUG DESIGN TOOL AND METHOD

PUBLICATION-DATE: January 24, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
GRASS, GEORGE M.	TAHOE CITY	CA	US	
LEESMAN, GLEN D.	HAMILTON	MT	US	
NORRIS, DANIEL A.	SAN DIEGO	CA	US	
SINKO, PATRICK J.	LEBANON	NJ	US	
WEHRLI, JOHN E.	MOUNTAIN VIEW	CA	US	

US-CL-CURRENT: 702/19; 435/283.1, 435/287.1, 702/22

ABSTRACT:

The present invention relates to a pharmacokinetic-based design and selection tool (PK tool) and methods for predicting absorption of an administered compound of interest. The methods utilize the tool, and optionally a separately operable component or subsystem thereof. The PK tool includes as computer-readable components: (1) input/output system; (2) physiologic-based simulation model of one or more segments of a mammalian system of interest having one or more physiological barriers to absorption that is based on the selected route of administration; and (3) simulation engine having a differential equation solver. The invention also provides methods for optimizing as well as enabling minimal input requirements a physiologic-based simulation model for predicting in vivo absorption, and optionally one or more additional properties, from either in vitro or in vivo data. The PK tool of the invention may be provided as a computer system, as an article of manufacture in the form of a computer-readable medium, or a computer program product and the like. Subsystems and individual components of the PK tool also can be utilized and adapted in a variety of disparate applications for predicting the fate of an administered compound. The PK tool and methods of the invention can be used to screen and design compound libraries, select and design drugs, as well as predict drug efficacy in mammals from in vitro and/or in vivo data of one or more compounds of interest. The PK tool and methods of the invention also finds use in selecting, designing, and preparing drug compounds, and multi-compound drugs and drug formulations (i.e., drug delivery system) for preparation of medicaments for use in treating mammalian disorders.

L2: Entry 1 of 2 File: PGPB Jan 24, 2002

DOCUMENT-IDENTIFIER: US 20020010550 A1
TITLE: PHARMACOKINETIC-BASED DRUG DESIGN TOOL AND METHOD

CLAIMS:

2. A computer-implemented method of predicting a pharmacokinetic property of a compound in a mammalian system of interest, said method comprising: providing a computer comprising as operably linked computer-implemented components an input/output system, a simulation engine, and a physiologic pharmacokinetic simulation model of two or more segments of a mammalian system of interest, wherein said simulation model comprises differential equations for calculating as a fuinction of time the change in (i) a physiological parameter of one or more of said segments and (ii) a pharmacokinetic property comprising an absorption parameter of a compound relative to a selected route of administration, barrier to absorption and sampling site of one or more of said segments, and wherein one or more of said differential equations is modified by a selectively optimized adjustment parameter; entering through said input/output system input data comprising dose, permeability and solubility data for said compound for one or more of said segments of said mammal system; and applying said simulation engine and said simulation model to predict a pharmacokinetic property of said compound in one or more segments of said mammal system of interest.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. D

☐ 2. Document ID: US 6542858 B1

L2: Entry 2 of 2 File: USPT Apr 1, 2003

US-PAT-NO: 6542858
DOCUMENT-IDENTIFIER: US 6542858 B1

TITLE: Pharmacokinetic-based drug design tool and method

DATE-ISSUED: April 1, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Grass; George M.	Tahoe City	CA		
Leesman; Glen D.	Hamilton	MT		
Norris; Daniel A.	San Diego	CA		
Sinko; Patrick J.	Lebanon	NJ		
Wehrli; John E.	Mountain View	CA		

US-CL-CURRENT: 703/2; 702/19, 703/11

ABSTRACT:

The present invention relates to a pharmacokinetic-based design and selection tool (PK tool) and methods for predicting absorption of an administered compound of interest. The methods utilize the tool, and optionally a separately operable component or subsystem thereof. The PK tool includes as computer-readable components: (1) input/output system; (2) physiologic-based simulation model of one or more segments of a mammalian system of interest having one or more physiological barriers to absorption that is based on the selected route of administration; and (3) simulation engine having a differential equation solver: The invention also provides methods for optimizing as well as enabling minimal input requirements a physiologic-based simulation model for predicting in vivo absorption, and optionally one or more additional properties, from either in vitro or in vivo data. The PK tool of the invention may be provided as a computer system, as an article of manufacture in the form of a computer-readable medium, or a computer program product and the like. Subsystems and individual components of the PK tool also can be utilized and adapted in a variety of disparate applications for predicting the fate of an administered compound. The PK tool and methods of the invention can be used to screen and design compound libraries, select and design drugs, as well as predict drug efficacy in mammals from in vitro and/or in vivo data of one or more compounds of interest. The PK tool and methods of the invention also finds use in selecting, designing, and preparing drug compounds, and multi-compound drugs and drug formulations (i.e., drug delivery system) for preparation of medicaments for use in treating mammalian disorders.

82 Claims, 58 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 39

L2: Entry 2 of 2 File: USPT Apr 1, 2003

DOCUMENT-IDENTIFIER: US 6542858 B1
TITLE: Pharmacokinetic-based drug design tool and method

CLAIMS:

1. A method of predicting a pharmacokinetic property of a compound in a first anatomical segment of a mammalian system from a pharmacokinetic property of the compound in a second anatomical segment of the mammalian system, the method comprising: providing a model, the model comprising at least one regional correlation parameter, wherein the at least one regional correlation parameter comprises a value obtained by: (i) assigning an initial value to the at least one regional correlation parameter of the model; (ii) inputting first data for a plurality of compounds in the second anatomical segment of the mammalian system into the model and running the model to generate output data; (iii) comparing the output data with second data for the plurality of compounds in the first anatomical segment of a mammalian system; (iv) selecting a new value for the at least one regional correlation parameter such that deviation of the comparison in step (iii) is reduced; and (v) replacing the value for the at least one regional correlation parameter in the model with the new value selected in step (iv); and using the model to predict the pharmacokinetic property of the compound in the first anatomical segment of the mammalian system from the pharmacokinetic property of the compound in the second anatomical segment of the mammalian system.

22. A method for optimizing at least one regional correlation parameter in a model for predicting a pharmacokinetic property of a compound in a first anatomical segment of a mammalian system from a pharmacokinetic property of the compound in a second anatomical segment of the mammalian system, the method comprising: (i) assigning an initial value to the at least one regional correlation parameter of the model; (ii) inputting first data for a plurality of compounds in the second

anatomical segment of the mammalian system into the model and running the model to generate output data; (iii) comparing the output data with second data for the plurality of compounds In the first anatomical segment of a mammalian system; (iv) selecting a new value for the at least one regional correlation parameter such that deviation of the comparison in step (iii) is reduced; and (v) replacing the value for the at least one regional correlation parameter with the new value selected in step (iv).

43. A computer readable device comprising: a computer readable medium; and a program generating a data structure on the computer readable medium containing a model for predicting a pharmacokinetic property of a compound in a first anatomical segment of a mammalian system from a pharmacokinetic property of the compound in a second anatomical segment of the mammalian system, the model comprising at least one regional correlation parameter, wherein the at least one regional correlation parameter comprises a value obtained by: (i) assigning an initial value to the at least one regional correlation parameter of the model; (ii) inputting data from a first data source into the model and running the model to generate output data, the first data source containing first data for a plurality of compounds in the second anatomical segment of the mammalian system; (iii) comparing the output data with a second data source, the second data source containing second data for the plurality of compounds in the first anatomical segment of a mammalian system; (iv) selecting a new value for the at least one regional correlation parameter such that deviation of the comparison in step (iii) is reduced; and (v) replacing the value for the at least one regional correlation parameter in the model with the new value selected in step (iv).

63. A computer system for predicting a pharmacokinetic property of a compound in a first anatomical segment of a mammalian system from a pharmacokinetic property of the compound in a second anatomical segment of the mammalian system, the computer system comprising: a computer; and a model running on the computer, the model comprising at least one regional correlation parameter, the at least one regional correlation parameter comprises a value obtained by: (i) assigning an initial value to the at least one regional correlation parameter of the model; (ii) inputting data from a first data source into the model and running the model to generate output data, the first data source containing first data for a plurality of compounds in the second anatomical segment of the mammalian system; (iii) comparing the output data with a second data source, the second data source containing second data for the plurality of compounds in the first anatomical segment of a mammalian system; (iv) selecting a new value for the at least one regional correlation parameter such that deviation of the comparison in step (iii) is reduced; and (v) replacing the value for at least one regional correlation parameter in the model with the new value selected in step (iv).

Term	Documents
TWO	6111606
TWOES	0
TWOS	2812

TWOE	13
MULTIPLE	1343941
MULTIPLES	41368
SECOND	4775361
SECONDS	442609
SITE	513821
SITES	286630
LOCATION	1247121
(L1 SAME ((TWO OR MULTIPLE OR SECOND) NEAR2 (SITE OR LOCATION OR SEGMENT))).PGPB,USPT,EPAB,JPAB,DWPI.	2

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 NEWS  4  May 12   Polymer links for the POLYLINK command completed in REGISTRY
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                   SDIs in CAplus
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L1           82 ("GRASS G"/AU OR "GRASS G M"/AU OR "GRASS G M IV"/AU OR "GRASS
                GEORGE"/AU OR "GRASS GEORGE M"/AU)

=> s l1 and pharmacokinetic
L2           30 L1 AND PHARMACOKINETIC

=> s l2 and model
L3           16 L2 AND MODEL

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L4   ANSWER 1 OF 10     MEDLINE on STN                    DUPLICATE 1
Full Text
AN   2002189771     MEDLINE
DN   PubMed ID: 11922957
TI   Physiologically-based pharmacokinetic simulation modelling.
AU   Grass George M; Sinko Patrick J
CS   LION bioscience, 9880 Campus Point Drive, San Diego, CA 92121, USA.
SO   Advanced drug delivery reviews, (2002 Mar 31) 54 (3) 433-51.  Ref: 134
     Journal code: 8710523. ISSN: 0169-409X.
CY   Netherlands
DT   Journal; Article; (JOURNAL ARTICLE)
     General Review; (REVIEW)
     (REVIEW, ACADEMIC)
LA   English
FS   Priority Journals
EM   200205
ED   Entered STN: 20020403
     Last Updated on STN: 20020522
     Entered Medline: 20020521
AB   Drug selection is now widely viewed as an important and relatively new,
     yet largely unsolved, bottleneck in the drug discovery and development
     process.  In order to achieve an efficient selection process, high
     quality, rapid, predictive and correlative ADME models are required in
     order for them to be confidently used to support critical financial
     decisions.  Systems that can be relied upon to accurately predict
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performance in humans have not existed, and decisions have been made using tools whose capabilities could not be verified until candidates went to clinical trial, leading to the high failure rates historically observed. However, with the sequencing of the human genome, advances in proteomics, the anticipation of the identification of a vastly greater number of potential targets for drug discovery, and the potential of pharmacogenomics to require individualized evaluation of drug kinetics as well as drug effects, there is an urgent need for rapid and accurately computed **pharmacokinetic** properties.

L4 ANSWER 2 OF 10 MEDLINE on STN DUPLICATE 2
Full Text
AN 2000165371 MEDLINE
DN PubMed ID: 10699270
TI Development of predictive **pharmacokinetic** simulation **models** for drug discovery.
AU Norris D A; Leesman G D; Sinko P J; **Grass G M**
CS Trega Biosciences, 9880 Campus Point Dr., San Diego, CA 92121, USA.. dnorris@trega.com
SO Journal of controlled release : official journal of the Controlled Release Society, (2000 Mar 1) 65 (1-2) 55-62.
Journal code: 8607908. ISSN: 0168-3659.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200005
ED Entered STN: 20000525
Last Updated on STN: 20000525
Entered Medline: 20000518
AB As discovery chemistry produces increased numbers of potential drug compounds, the use of ADME (absorption, distribution, metabolism, and excretion) properties is becoming increasingly important in the drug selection and promotion process. A computer simulation **model** has been developed and validated to predict ADME outcomes, such as rate of absorption, extent of absorption, etc. using a limited number of in vitro data inputs. The oral bioavailability of ganciclovir in dogs and humans was simulated using a physiologically based **model** that utilized many biopharmaceutically relevant parameters, such as the concentration of ganciclovir in the duodenum, jejunum, ileum, and colon at various dose levels and solubility values. The simulations were run and compared to dog and human in vivo data. The simulation results demonstrated that the low bioavailability of ganciclovir is limited by compound solubility rather than permeability due to partitioning as previously speculated. This technology provides a breakthrough in in silico prediction of absorption and with its continued development and improvement, will aid drug discovery and development scientists to produce better pharmaceutical products.

L4 ANSWER 3 OF 10 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
Full Text
AN 1994:428028 BIOSIS
DN PREV199497441028
TI A mathematical **model** to predict oral drug absorption from in vitro permeability studies.
AU **Grass, G. M.**
CS Precision Instrument Design Inc., Tahoe City, CA, USA
SO In Vitro Toxicology, (1994) Vol. 7, No. 2, pp. 168.
Meeting Info.: World Congress on Alternatives and Animal Use in the Life Sciences. Baltimore, Maryland, USA. November 14-19, 1993.

CODEN: IVTOE4. ISSN: 0888-319X.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 3 Oct 1994
Last Updated on STN: 4 Oct 1994

L4 ANSWER 4 OF 10 MEDLINE on STN DUPLICATE 3
Full Text
AN 93279942 MEDLINE
DN PubMed ID: 8505206
TI A **model** to predict aqueous humor and plasma **pharmacokinetics** of ocularly applied drugs.
AU **Grass G M**; Lee V H
CS Precision Instrument Design, Inc., Tahoe City, California.
NC EY7389 (NEI)
SO Investigative ophthalmology & visual science, (1993 Jun) 34 (7) 2251-9.
Journal code: 7703701. ISSN: 0146-0404.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199307
ED Entered STN: 19930716
Last Updated on STN: 19930716
Entered Medline: 19930707
AB PURPOSE. To develop methods for constructing a **pharmacokinetic model** to predict the time course of aqueous humor and plasma drug concentrations after topical dosage in rabbits using the simulation program iThink (formerly STELLA; High Performance Systems, Lyme, NH). METHOD. The **model** was constructed in experimentally verifiable segments using previously published data on intravenous, nasal, and ocular dosage, and was used to describe the influence of prolonging precorneal retention and varying drug release rate on the ratio of drug absorbed locally to drug absorbed systemically in rabbits. RESULTS. The **model** developed is comprehensive; it includes precorneal kinetics, nasal absorption kinetics, and plasma kinetics. CONCLUSIONS. Such a **model** may be useful in designing drug delivery strategies to improve the safety of topical eye medications through minimization of systemic absorption and maximization of drug delivery to ocular tissues.

L4 ANSWER 5 OF 10 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
Full Text
AN 1993:69135 BIOSIS
DN PREV199344034785
TI A **pharmacokinetic model** to predict aqueous humor and plasma drug concentrations from topical dosing to the eye.
AU **Grass, George M.** [Reprint author]; Lee, Vincent H.-L.
CS Precision Instrument Design, Inc., Tahoe City, Calif, USA
SO Pharmaceutical Research (New York), (1992) Vol. 9, No. 10 SUPPL., pp. S335.
Meeting Info.: American Association of Pharmaceutical Scientists 1992 Annual Meeting and Exposition. San Antonio, Texas, USA. November 15-19, 1992.
CODEN: PHREEB. ISSN: 0724-8741.
DT Conference; (Meeting)
LA English
ED Entered STN: 15 Jan 1993
Last Updated on STN: 15 Jan 1993

L4 ANSWER 6 OF 10 MEDLINE on STN
Full Text
AN 90218611 MEDLINE
DN PubMed ID: 1969948
TI The effects of enprostil and RS-86505-007 on in-vitro intestinal permeability of rabbit and monkey.
AU **Grass G M**; Sweetana S A; Bozarth C A
CS Institute of Pharmaceutical Sciences, Syntex Research, Palo Alto, CA 94303.
SO Journal of pharmacy and pharmacology, (1990 Jan) 42 (1) 40-4.
Journal code: 0376363. ISSN: 0022-3573.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199005
ED Entered STN: 19900622
Last Updated on STN: 19970203
Entered Medline: 19900524
AB Enprostil is a prostaglandin E2 analogue characterized as a racemic mixture of four stereoisomers. Enprostil and a single isomer, RS-86505-007, were evaluated for their effects on the permeability of actively and passively transported compounds in segments of small intestine from rabbits and monkeys. Consistent with human in-vivo studies, which have demonstrated decreases in absorption of D-xylose, both compounds inhibited D-glucose transport. The passively transported compounds mannitol and progesterone were also less permeable in this **model** in the presence of enprostil or RS-86505-007. In contrast to the concentration-dependent inhibition displayed by ouabain, RS-86505-007 had no effect on purified Na+K(+)-ATPase. It is suggested that an effect of a general nature, possibly an increase in the barrier properties at the intestinal surface, may explain the transport inhibition. Of two other enprostil isomers, RS-86812-007 inhibited D-glucose transport in rabbit small intestine, while RS-86505-008 had no effect. The prostaglandin E1 analogue misoprostol was ineffective in monkey and poorly effective in rabbit. This suggests that the inhibition of D-glucose transport by enprostil and its active stereoisomers is mediated through some structurally specific receptor interaction.

L4 ANSWER 7 OF 10 MEDLINE on STN
Full Text
AN 90046389 MEDLINE
DN PubMed ID: 2554270
TI Evidence for site-specific absorption of a novel ACE inhibitor.
AU **Grass G M**; Morehead W T
CS Institute of Pharmaceutical Sciences, Syntex Research, Palo Alto, California 94303.
SO Pharmaceutical research, (1989 Sep) 6 (9) 759-65.
Journal code: 8406521. ISSN: 0724-8741.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198912
ED Entered STN: 19900328
Last Updated on STN: 19900328
Entered Medline: 19891221
AB Moexipril [2-[(1-ethoxycarbonyl)-3-phenylpropyl]amino-1-oxopropyl]-6, 7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (S,S,S)], an ester prodrug of an ACE inhibitor, was formulated in controlled-release

preparations with a range of in vitro release rates, to provide a prolonged input of drug in vivo. However, **pharmacokinetic** studies with the controlled-release dosage forms in humans produced plasma profiles with the same characteristics and time to peak as an immediate-release capsule. In vitro dissolution data from the controlled-release dosage form, as well as the known characteristics of the polymer used to control drug release from the dosage form, suggest no reason to suspect an abrupt halt to the in vivo release of the drug after 1-2 hr. The lack of sustained blood levels is, therefore, most likely due to failure of the GI tract to absorb the drug beyond some location in the upper small intestine, i.e., site-specific absorption. This theory is supported by a series of computer simulations involving moexipril and the active moiety, moexipril diacid. Possible mechanisms include poor drug permeability, a pH effect whereby the zwitterionic form of the drug is more rapidly absorbed, and esterase cleavage of moexipril to the poorly absorbed moexipril diacid.

L4 ANSWER 8 OF 10 MEDLINE on STN DUPLICATE 4
Full Text
AN 88155337 MEDLINE
DN PubMed ID: 3346819
TI Mechanisms of corneal drug penetration. III: Modeling of molecular transport.
AU **Grass G M**; Cooper E R; Robinson J R
CS University of Wisconsin-Madison 53706.
SO Journal of pharmaceutical sciences, (1988 Jan) 77 (1) 24-6.
Journal code: 2985195R. ISSN: 0022-3549.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198804
ED Entered STN: 19900308
Last Updated on STN: 19900308
Entered Medline: 19880412
AB A **model** relating the parameters of permeability coefficient in the cornea with partition coefficient and molecular weight of the penetrating species is presented. The development of the **model** is unique in that it includes the availability of a "pore" pathway with the corresponding kinetic data to substantiate this premise. The "pore" pathway is applied to small hydrophilic compounds and assumes that an aqueous diffusional space is available for transport of these compounds. This is in contrast to an alternate "partitioning" mechanism which is the most probable route of transport for larger or more lipophilic entities. The **model** is consistent with published data from this and other laboratories.

L4 ANSWER 9 OF 10 MEDLINE on STN DUPLICATE 5
Full Text
AN 88155336 MEDLINE
DN PubMed ID: 3346818
TI Mechanisms of corneal drug penetration. II: Ultrastructural analysis of potential pathways for drug movement.
AU **Grass G M**; Robinson J R
CS University of Wisconsin-Madison 53706.
SO Journal of pharmaceutical sciences, (1988 Jan) 77 (1) 15-23.
Journal code: 2985195R. ISSN: 0022-3549.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals

EM 198804
ED Entered STN: 19900308
Last Updated on STN: 19970203
Entered Medline: 19880412
AB Ultrastructure analysis was conducted in an effort to augment the results of classical kinetic studies. Scanning electron microscopy (SEM) allowed visual inspection of cellular junctions on corneal epithelium and endothelium. The addition of calcium-chelating agents to in vivo and in vitro mounted corneas demonstrated a concentration-dependent progressive expansion of the intercellular spaces of epithelium and endothelium, as seen by SEM. The expansion of these cellular junctions correlates with increases in permeability of the cornea to glycerol under similar conditions. The size of the intercellular space was estimated by transmission electron microscopy. Use of lanthanum as a marker of aqueous diffusional pathways demonstrated that the epithelial surface is not a totally occlusive barrier to transport of small hydrophilic compounds. Development of a method whereby an administered drug could be visualized in its actual pathway of movement through the cornea was undertaken, involving precipitation of specific compounds in the tissue with osmium tetroxide vapor. Results suggest that separate pathways of drug movement exist in the cornea for hydrophilic and hydrophobic compounds. Hydrophilic compounds were preferentially located in intercellular spaces, whereas hydrophobic compounds were associated with the lipid structures of the tissue. The results of these studies are consistent with a currently proposed 'pore' **model** for the penetration of drugs through the cornea.

L4 ANSWER 10 OF 10 MEDLINE on STN DUPLICATE 6
Full Text
AN 88155339 MEDLINE
DN PubMed ID: 3126290
TI Mechanisms of corneal drug penetration. I: In vivo and in vitro kinetics.
AU **Grass G M**; Robinson J R
CS University of Wisconsin-Madison 53706.
SO Journal of pharmaceutical sciences, (1988 Jan) 77 (1) 3-14.
Journal code: 2985195R. ISSN: 0022-3549.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198804
ED Entered STN: 19900308
Last Updated on STN: 19980206
Entered Medline: 19880412
AB Corneal penetration studies were conducted in unanesthetized albino rabbits using various organic compounds representing both polar and nonpolar species. Very low molecular weight compounds demonstrate rapid uptake into the aqueous humor despite the lipid-like barrier imposed by the corneal epithelium. Evidence that these compounds may have access to a diffusional channel for corneal transport is presented. In vitro permeability studies were also conducted in an effort to quantitate the corneal diffusion of compounds covering a range of molecular weights and partition coefficients; the results corresponded well with the results of in vivo experiments. Calculations of energies of activation, taken from Arrhenius plots, indicate that the diffusion of drug across the cornea may be by two different mechanisms that depend on the physical-chemical characteristics of the perfusant. One mechanism appears similar to drug movement in an aqueous environment and is characterized by an activation energy similar to that for diffusion in water. The other relates to the expected partitioning of a compound across cellular membranes represented by a relatively high activation energy for diffusion. For hyrdophilic

compounds, the epithelium appears to be rate limiting to drug movement, whereas for hydrophobic compounds, the stroma is rate limiting. In the presence of calcium-chelating agents, glycerol demonstrated an increase in corneal penetration in vivo. This effect appears to be reversible at specific concentrations of chelator. In contrast, divalent cations reduced corneal penetration of glycerol. The known calcium chelator EDTA was shown to penetrate the cornea, conjunctiva, and iris/ciliary body from a topically applied dose. The implications of this observation pertain to toxicity effects when EDTA is incorporated into ocular drug products for stability purposes, or novel stratagems for improving ocular bioavailability of topically applied drugs are employed. The addition of calcium-chelating agents to in vivo mounted corneas demonstrated increases in permeability of the cornea to glycerol which were directly related to the concentration of chelating agent used. These results paralleled the findings of similar in vivo studies. The results of these studies are consistent with a currently proposed 'pore' **model** for the penetration of drugs through the cornea which demonstrates both a partition coefficient and molecular weight dependency on the permeability of the cornea to transported compounds.

```
=> s pharmacokinetics
L5      298097 PHARMACOKINETICS

=> s l5 and model
L6       46611 L5 AND MODEL

=> s l6 and predict
L7        2074 L6 AND PREDICT

=> s l6 and predict?
L8        6486 L6 AND PREDICT?

=> s l6 and ((two or multiple or second) (2A) (site or location or organ or
segment))
L9         313 L6 AND ((TWO OR MULTIPLE OR SECOND) (2A) (SITE OR LOCATION OR
               ORGAN OR SEGMENT))

=> s l9 and py<1998
L10        165 L9 AND PY<1998

=> duplicate remove l10
DUPLICATE PREFERENCE IS 'MEDLINE, BIOSIS'
KEEP DUPLICATES FROM MORE THAN ONE FILE?  Y/(N):n
PROCESSING COMPLETED FOR L10
L11        142 DUPLICATE REMOVE L10 (23 DUPLICATES REMOVED)

=> d 1-10 bib ab

L11  ANSWER 1 OF 142     MEDLINE on STN
Full Text
AN   1998090335     MEDLINE
DN   PubMed ID: 9430470
TI   Radiation dosimetry for indium-111-pentetreotide.
AU   Stabin M G; Kooij P P; Bakker W H; Inoue T; Endo K; Coveney J; de Jong R;
     Minegishi A
CS   Oak Ridge Institute for Science and Education, Tennessee 37831-0117, USA.
SO   Journal of nuclear medicine : official publication, Society of Nuclear
     Medicine, (1997 Dec) 38 (12) 1919-22.
     Journal code: 0217410. ISSN: 0161-5505.
```

CY United States
DT Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
LA English
FS Priority Journals
EM 199802
ED Entered STN: 19980217
Last Updated on STN: 19990129
Entered Medline: 19980205
AB We present radiation dose estimates for 111In-pentetreotide. METHODS: Kinetic data were gathered in 10 subjects at **two** different **sites**. A compartmental **model** was used to fit the data, including retention, in three major organs and excretion. RESULTS: The data were consistent for the subjects at both sites. The organ receiving the highest dose was the kidneys (0.52 mGy/MBq); the effective dose equivalent was 0.1 mSv/MBq, and the effective dose was 0.073 mSv/MBq. CONCLUSION: The results of this study provide the basis for evaluation of radiation safety of this drug.

L11 ANSWER 2 OF 142 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
Full Text
AN 1998:125617 BIOSIS
DN PREV199800125617
TI Moment analysis of intestinal first-pass metabolism by portal-systemic concentration difference in single conscious rat using 5'-deoxy-5-fluorouridine and 5-fluorouracil as **model** drug system.
AU Sawai, Yoneichi; Yamaoka, Kiyoshi [Reprint author]; Takemura, Arisa; Nakagawa, Terumichi
CS Fac. Pharm. Sci., Kyoto Univ., Sakyo-ku, Kyoto 606, Japan
SO Journal of Pharmaceutical Sciences, (Nov., 1997) Vol. 86, No. 11, pp. 1269-1272. print.
CODEN: JPMSAE. ISSN: 0022-3549.
DT Article
LA English
ED Entered STN: 5 Mar 1998
Last Updated on STN: 5 Mar 1998
AB Intestinal first-pass metabolism was evaluated in a single conscious rat based on a difference in concentrations of parent drug and its metabolite between the portal and systemic bloods (P-S difference method). 5'-Deoxy-5-fluorouridine (5'-DFUR) and 5-fluorouracil (5-FU) were selected as **model** drug (prodrug of 5-FU) and metabolite pair. The portal vein and the femoral artery of the rat were cannulated so blood samples could be obtained simultaneously from the **two sites**. 5'-DFUR (100 mg/kg) was administered intraarterially or orally. Concentrations of 5'-DFUR and 5-FU in the portal and arterial samples were assayed by HPLC. The concentration-time profiles of 5'-DFUR and 5-FU were analyzed by local moment analysis. The extent of systemic bioavailability (F) of 5'-DFUR was estimated to be 75.8%. After oral administration, the local absorption ratio (Fa) and the mean local absorption time (ta) of 5'-DFUR were estimated to be 65.8 +- 7.3% of dose and 74.0 +- 21.7 min, respectively. The Fa value was close to F, which suggests that the metabolic conversion from 5'-DFUR to 5-FU is not extensive in the liver. The mean absorption time (MAT), calculated to be 76.3 min, almost coincided with ta, which suggests that the mean hepatic transit time is negligible in this experimental scale. The local absorption ratio of metabolite (Fam) was 6.8 +- 1.7% of orally administered 5'-DFUR, which means that ~7% of 5'-DFUR arrived as 5-FU at the portal system. The mean local absorption time (tam) of 5-FU was estimated to be 75.5 min, which is close to that (74.0 min) of 5'-DFUR. Local moment analysis based on P-S difference enabled simultaneous estimation of the local absorption kinetics of a parent compound and the intestinal generation of metabolites

by separating the intestinal first-pass metabolism of a drug from the subsequent disposition through the liver and in the systemic circulation.

L11 ANSWER 3 OF 142 MEDLINE on STN
Full Text
AN 97324519 MEDLINE
DN PubMed ID: 9180624
TI Renin-angiotensin system components in the interstitial fluid of the isolated perfused rat heart. Local production of angiotensin I.
AU de Lannoy L M; Danser A H; van Kats J P; Schoemaker R G; Saxena P R; Schalekamp M A
CS Department of Internal Medicine, Erasmus University Rotterdam, Netherlands.
SO Hypertension, **(1997 Jun)** 29 (6) 1240-51.
Journal code: 7906255. ISSN: 0194-911X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199707
ED Entered STN: 19970721
Last Updated on STN: 19970721
Entered Medline: 19970703
AB We used a modification of the isolated perfused rat heart, in which coronary effluent and interstitial transudate were separately collected, to investigate the uptake and clearance of exogenous renin, angiotensinogen, and angiotensin I (Ang I) as well as the cardiac production of Ang I. The levels of these compounds in interstitial transudate were considered to be representative of the levels in the cardiac interstitial fluid. During perfusion with renin or angiotensinogen, the steady-state levels (mean +/- SD) in interstitial transudate were 64 +/- 34% ($P < .05$ for difference from the arterial level, $n = 8$) and 108 +/- 42% ($n = 6$) of the arterial level, respectively; the levels in coronary effluent were not significantly different from those in interstitial transudate. Ang I was not detectable in interstitial transudate during perfusion with Tyrode's buffer or angiotensinogen. It was very low in interstitial transudate during perfusion with renin and rose to much higher levels during combined renin and angiotensinogen perfusion. The total production rate of Ang I present in interstitial fluid could be largely explained by the renin-angiotensinogen reaction in the fluid phase of the interstitial compartment. In contrast, the total production rate of Ang I present in coronary effluent and the net ejection rate of Ang I via coronary effluent were, respectively, 4.6 +/- 2.2 and 2.8 +/- 1.3 ($P < .01$ and $P < .05$ for difference from 1.0, $n = 6$) times higher than could be explained by Ang I formation in the fluid phase of the intravascular compartment. Ang I from the interstitial fluid contributed little to the Ang I in the intravascular fluid and vice versa. These data reveal **two** tissue **sites** of Ang I production, ie, the interstitial fluid and a site closer to the blood compartment, possibly vascular surface-bound renin. There was no evidence that the release of locally produced Ang I into coronary effluent and interstitial transudate occurred independently of blood-derived renin or angiotensinogen.

L11 ANSWER 4 OF 142 MEDLINE on STN
Full Text
AN 97426244 MEDLINE
DN PubMed ID: 9282948
TI Brain and spinal cord distribution of biphalin: correlation with opioid receptor density and mechanism of CNS entry.

AU Abbruscato T J; Thomas S A; Hruby V J; Davis T P
CS Department of Pharmacology, University of Arizona, College of Medicine, Tucson 85724, U.S.A.
NC DA-06284 (NIDA)
SO Journal of neurochemistry, **(1997 Sep)** 69 (3) 1236-45.
Journal code: 2985190R. ISSN: 0022-3042.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199709
ED Entered STN: 19971008
Last Updated on STN: 19971008
Entered Medline: 19970925
AB Biphalin [(Tyr-D-Ala-Gly-Phe-NH)2] is a bivalent, opioid peptide containing two pharmacophores linked by a hydrazine bridge. When administered intracerebroventricularly, it has been shown to be more potent than morphine and etorphine at eliciting antinociception. Biphalin has also been shown to cross both the blood-brain and blood-cerebrospinal fluid barriers. To understand the basis of biphalin's potency, regional brain and spinal cord distribution studies with [125I-Tyr1]biphalin were performed 5, 20, and 40 min after intravenous bolus injections. A statistically greater amount of [125I-Tyr1]biphalin was detected in the nucleus accumbens compared with other brain regions ($p < 0.05$). This correlates with the high density of delta- and mu-opioid receptor mRNA and binding sites shown to be expressed in the nucleus accumbens. Also, a statistically greater amount of [125I-Tyr1] biphalin was detected in **two** other circumventricular **organs**, the choroid plexus and pituitary, when compared with other brain regions. These studies provide evidence that biphalin can reach not only brain sites, but also spinal sites to elicit antinociception. The overall CNS distribution of [125I-Tyr1]biphalin was decreased with naloxone, D-Phe-Cys-Tyr-D-Trp-Arg-Thr-Pen-Thr-NH2, or naltrindole pretreatment, showing that biphalin detected in the brain and spinal cord is binding to delta- and mu-opioid receptors. Additional in situ brain perfusion experiments identified a saturable component contributing to CNS entry of [125I-Tyr1]biphalin, which could be described by Michaelis-Menten kinetics with a Km of 2.6 +/- 4.8 microM, Vmax of 14.6 +/- 2.89 pmol(-1) x min(-1) x g(-1), and Kd of 0.568 +/- 0.157 microl x min(-1) x g(-1). Brain entry of [125I-Tyr1]biphalin was sensitive to 2-aminobicyclo[2.2.1]heptane-2-carboxylic acid and L-phenylalanine, suggesting use of the large neutral amino acid carrier. This work provides evidence that biphalin is a promising, potent analgesic that has a unique mechanism for reaching both spinal and supraspinal opioid receptor sites.

L11 ANSWER 5 OF 142 MEDLINE on STN DUPLICATE 1
Full Text
AN 97452355 MEDLINE
DN PubMed ID: 9308769
TI An experimental **multiple-organ model** for the study of regional net release/uptake rates of tissue-type plasminogen activator in the intact pig.
AU Jern C; Seeman-Lodding H; Biber B; Winso O; Jern S
CS Heart and Lung Institute, Department of Neurology, Sahlgrenska University Hospital, Goteborg University, Sweden.
SO Thrombosis and haemostasis, **(1997 Sep)** 78 (3) 1150-6.
Journal code: 7608063. ISSN: 0340-6245.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English

FS Priority Journals; Space Life Sciences
EM 199801
ED Entered STN: 19980129
Last Updated on STN: 19980129
Entered Medline: 19980114
AB Experimental data indicate large between-organs variations in rates of synthesis of tissue-type plasminogen activator (t-PA), which may reflect important differences in the capacity for constitutive and stimulated t-PA release from the vascular endothelium. In this report we describe a new **multiple-organ** experimental in vivo **model** for simultaneous determinations of net release/uptake rates of t-PA across the coronary, splanchnic, pulmonary, and hepatic vascular beds. In eleven intact anesthetized pigs, blood samples were obtained simultaneously from the proximal aorta, coronary sinus, pulmonary artery, and portal and hepatic veins. Plasma flows were monitored separately for each vascular region. Total plasma t-PA was determined by ELISA with a porcine t-PA standard. Regional net release/uptake rates were defined as the product of arteriovenous concentration gradients and local plasma flows. The net release of t-PA across the splanchnic vascular bed was very high, with a mean output of 1,919 ng total t-PA x min(-1) (corresponding to 90 ng per min and 100 g tissue). The net coronary t-PA release was 68 ng x min(-1) (30 ng x min(-1) X 100 g(-1)). Pulmonary net fluxes of t-PA were variable without any significant net t-PA release. The net hepatic uptake rate was 4,855 ng x min(-1) (436 ng x min(-1) x 100 g(-1)). Net trans-organ changes of active t-PA mirrored those of total t-PA. The results demonstrate marked regional differences in net release rates of t-PA in vivo. The experimental **model** we present offers new possibilities for evaluation of regional secretion patterns in the intact animal.

L11 ANSWER 6 OF 142 MEDLINE on STN
Full Text
AN 97175663 MEDLINE
DN PubMed ID: 9023318
TI The effect of inhibitors of inducible nitric oxide synthase on chronic colitis in the rhesus monkey.
AU Ribbons K A; Currie M G; Connor J R; Manning P T; Allen P C; Didier P; Ratterree M S; Clark D A; Miller M J
CS Department of Pediatrics, Louisiana State University Medical Center, New Orleans 70112, USA.
NC 223-94-1100 (NCRR)
2P51-RR-AG00169 (NCRR)
5P51-RR00164
SO Journal of pharmacology and experimental therapeutics, **(1997 Feb)** 280 (2) 1008-15.
Journal code: 0376362. ISSN: 0022-3565.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199703
ED Entered STN: 19970327
Last Updated on STN: 19970327
Entered Medline: 19970317
AB GI inflammation is associated with an increase in nitric oxide production and expression of the inducible isoform of nitric oxide synthase (iNOS). Using a spontaneous **model** of chronic colonic inflammation in rhesus monkeys, which shares morphological and clinical features with ulcerative colitis, we assessed the therapeutic benefit of administration of iNOS inhibitors. Sixteen colitic rhesus monkeys underwent an endoscopy procedure before commencement of the trial, and biopsies from three sites

of the colon and plasma were collected. Monkeys were randomly assigned to three treatment groups and were administered by oral bolus 60 mg/kg/day L-N 6-(1-Iminoethyl) lysine, 60 mg/kg/day aminoguanidine or a placebo (0.9% NaCl) twice daily. Monkeys were sacrificed after 10 days, colonic tissue from **multiple sites** was dissected and processed for histological and biochemical analysis. In rhesus colitis, diarrhea was characterized by a significant increase in fecal water content and daily fecal output. iNOS was localized immunohistochemically in plasma cells and neutrophils in the colonic mucosa and lamina propria, paralleled by enhanced iNOS gene expression determined by reverse-transcriptase polymerase chain reaction. Only L-N 6-(1-iminoethyl) lysine administration resulted in a significant reduction in systemic nitric oxide production, and neither of the iNOS inhibitors significantly reduced the histological inflammatory score nor ameliorated diarrheal symptoms. From these findings, we conclude that in this chronic, spontaneous **model** of colonic inflammation, administering iNOS inhibitors with this treatment regimen did not provide any major therapeutic benefit.

L11 ANSWER 7 OF 142 MEDLINE on STN
Full Text
AN 1998097972 MEDLINE
DN PubMed ID: 9435683
TI Identification of Mg-transporting renal tubules and cells by ion microscopy imaging of stable isotopes.
AU Chandra S; Morrison G H; Beyenbach K W
CS Department of Chemistry, Cornell University, Ithaca, New York 14853, USA.
NC GM-24314 (NIGMS)
SO American journal of physiology, **(1997 Dec)** 273 (6 Pt 2) F939-48.
Journal code: 0370511. ISSN: 0002-9513.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199802
ED Entered STN: 19980224
Last Updated on STN: 19980224
Entered Medline: 19980209
AB Sites of renal Mg transport were identified in seawater killifish (Fundulus heteroclitus) using a Cameca **model** IMS-3f ion microscope. Killifish were given an intraperitoneal injection of the stable isotope 26Mg (99.5% enrichment) to stimulate and trace renal Mg excretion. We identified **two sites** of 26Mg transport in frozen freeze-dried cryosections of kidney: the proximal tubule, known to secrete Mg, and the collecting duct, heretofore not known to handle Mg. In epithelial cells of the proximal tubule, the punctate distribution of injected 26Mg suggests transcytotic excretion of Mg in bound form. In collecting ducts, a subpopulation of Mg/Ca-rich cells was identified with high accumulations of injected 26Mg. Here, the punctate distribution of 26Mg decreased from the apical to the basal region of the cells, revealing a transcytotic gradient of apparently bound Mg. Since proximal tubules of fish are implicated with Mg secretion, Mg/Ca-rich cells in the collecting duct may reabsorb Mg, thereby providing the usual two-step of renal regulation, now also for Mg.

L11 ANSWER 8 OF 142 MEDLINE on STN
Full Text
AN 1998088334 MEDLINE
DN PubMed ID: 9426897
TI Measurement of sodium fluorescein wash-in time constants in subjects with peripheral vascular disease.

AU Oh D K; Zhang A; Magin R L
CS Center for Biophysics and Computational Biology, University of Illinois Beckman Institute for Advanced Science and Technology, Urbana 61801, USA.
SO Biomedical instrumentation & technology / Association for the Advancement of Medical Instrumentation, **(1997 Nov-Dec)** 31 (6) 600-7.
Journal code: 8905560. ISSN: 0899-8205.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199802
ED Entered STN: 19980217
Last Updated on STN: 19980217
Entered Medline: 19980203
AB The authors developed a noninvasive two-channel dynamic dermofluorometer that can quantitatively follow the rapid skin wash-in kinetics of a fluorescent dye to provide an assessment of local skin perfusion. The dermofluorometer was tested in normal subjects and diabetic patients with and without peripheral vascular disease. After an intravenous injection of 1-2 mL of a 10% solution of sodium fluorescein (1.1-2.8 mg/kg), the fluorescent signal was monitored from **two sites** on the skin surfaces of the forearm and foot. A 3.2-mm-diameter glass fiberoptic bundle was used both to transmit the excitation light (489 nm) and to receive the fluorescent emission (517 nm). Dermofluorometer readings were recorded approximately every second for 10-15 minutes following the injection. The time course of the fluorescein signal intensity was fit to a single exponential curve characterized by a wash-in time constant. There was no significant difference in arm wash-in time constants. Foot wash-in time constants were increased in diabetic patients who had past histories of foot ulcers relative to diabetic patients without a history of foot ulcers (3.2 vs 1.6 min., $p < 0.05$). Foot wash-in time constants were decreased in diabetic patients who had active infected foot ulcers. This study demonstrates the ability of the dynamic dermofluorometer to measure wash-in constants that reflect the local skin perfusion in less than 15 minutes after a low intravenous dose of sodium fluorescein.

L11 ANSWER 9 OF 142 MEDLINE on STN
Full Text
AN 1998069510 MEDLINE
DN PubMed ID: 9406436
TI Ouabain-sensitive Na+,K(+)-ATPase activity in toad brain.
AU Morris J F; Ismail-Beigi F; Butler V P Jr; Gati I; Lichtstein D
CS Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, NY 10032, USA.
NC GM 39835 (NIGMS)
HL 10608 (NHLBI)
HL 18708 (NHLBI)
SO Comparative biochemistry and physiology. Part A, Physiology, **(1997 Nov)** 118 (3) 599-606.
Journal code: 9516062. ISSN: 1096-4940.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199802
ED Entered STN: 19980226
Last Updated on STN: 19980226
Entered Medline: 19980218
AB Toads of the genus Bufo are highly resistant to the toxic effects of digitalis glycosides, and the Na+,K(+)-ATPase of all toad tissues studied

to date has been relatively insensitive to inhibition by digitalis and related compounds. In studies of brain microsomal preparations from two toad species, Bufo marinus and Bufo viridis, inhibition of ATPase activity and displacement of [3H]ouabain from Na+,K(+)-ATPase occurred over broad ranges of ouabain or bufalin concentrations, consistent with the possibility that more than one Na+,K(+)-ATPase isoform may be present in toad brain. The data could be fitted to one- or **two-site models**, both of which were consistent with the presence of Na+,K(+)-ATPase activity with high sensitivity to ouabain and bufalin. Ki (concentration capable of producing 50% inhibition of activity) values for ouabain in the one-site **model** were in the 0.2 to 3.7 microM range, whereas Ki1 values in the **two-site model** ranged from 0.085 to 0.85 microM, indicating that brain ATPase was at least three orders of magnitude more sensitive to ouabain than B. marinus bladder ATPase (Ki = 5940 microM). Ouabain was also an effective inhibitor of 86Rb+ uptake in B. marinus brain tissue slices (Ki = 3.1 microM in the one-site **model**; Ki1 = 0.03 microM in the **two-site model**). However, the relative contribution of the high ouabain-sensitivity site to the total activity was 17% in the transport assay as compared with 63% in the Na+,K(+)-ATPase enzymatic assay. We conclude that a highly ouabain-sensitive Na+,K(+)-ATPase activity is present and functional in toad brain but that its function may be partially inhibited in vivo.

L11 ANSWER 10 OF 142 MEDLINE on STN
Full Text
AN 1998032608 MEDLINE
DN PubMed ID: 9365904
TI Cation permeability of a cloned rat epithelial amiloride-sensitive Na+ channel.
AU Ismailov I I; Shlyonsky V G; Alvarez O; Benos D J
CS Department of Physiology and Biophysics, University of Alabama at Birmingham 35294-0005, USA.. Ismailov@PhyBio.bhs.uab.Edu
NC DK 37206 (NIDDK)
SO Journal of physiology, **(1997 Oct 15)** 504 (Pt 2) 287-300.
Journal code: 0266262. ISSN: 0022-3751.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199801
ED Entered STN: 19980129
Last Updated on STN: 19980129
Entered Medline: 19980113
AB 1. Conductance of heterotrimeric rat epithelial Na+ channels (alpha, beta, gamma-rENaCs) for Li+ and Na+ in planar lipid bilayers was a non-linear function of ion concentration, with a maximum of 30.4 +/- 2.9 pS and 18.5 +/- 1.9 pS at 1 M Li+ and Na+, respectively. 2. The alpha, beta, gamma-rENaC conductance measured in symmetrical mixtures of Na(+)-Li+ (1 M) exhibited an anomalous mole fraction dependence, with a minimum at 4:1 Li+ to Na+ molar ratio. 3. Permeability ratios PK/PNa and PLi/PNa of the channel calculated from the bionic reversal potentials were dependent on ion concentration: PK/PNa was 0.11 +/- 0.01, and PLi/PNa was 1.6 +/- 0.3 at 50 mM; PK/PNa was 0.04 +/- 0.01 and PLi/PNa was 2.5 +/- 0.4 at 3 M, but differed from the ratios of single-channel conductances in symmetrical Li+, Na+ or K+ solutions. The permeability sequence determined by either method was Li+ > Na+ > K+ >> Rb+ Cs+. 4. Predictions of a **model** featuring **two** binding **sites** and three energy barriers (2S3B), and allowing double occupancy, developed on the basis of single ion current-voltage relationships, are in agreement with the observed conductance maximum in single ion experiments, conductance minimum in the

mole fraction experiments, non-linearity of the current-voltage curves in bionic experiments, and the concentration dependence of permeability ratios. 5. Computer simulations using the 2S3B **model** recreate the ion concentration dependencies of single-channel conductance observed for the immunopurified bovine renal amiloride-sensitive Na+ channel, and short-circuit current in frog skin, thus supporting the hypothesis that ENaCs form a core conduction unit of epithelial Na+ channels.

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     FILE 'MEDLINE, BIOSIS' ENTERED AT 13:37:43 ON 05 AUG 2004
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L1            82 S E3-E7
L2            30 S L1 AND PHARMACOKINETIC
L3            16 S L2 AND MODEL
L4            10 DUPLICATE REMOVE L3 (6 DUPLICATES REMOVED)
L5        298097 S PHARMACOKINETICS
L6         46611 S L5 AND MODEL
L7          2074 S L6 AND PREDICT
L8          6486 S L6 AND PREDICT?
L9           313 S L6 AND ((TWO OR MULTIPLE OR SECOND) (2A) (SITE OR LOCATION O
L10          165 S L9 AND PY<1998
L11          142 DUPLICATE REMOVE L10 (23 DUPLICATES REMOVED)

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L8 IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

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L12           43 L8 AND ((TWO OR MULTIPLE OR SECOND) (2A) (SITE OR LOCATION OR
                 SEGMENT))

=> s l12 and py<1998
L13           22 L12 AND PY<1998

=> duplicate remove l13
DUPLICATE PREFERENCE IS 'MEDLINE, BIOSIS'
KEEP DUPLICATES FROM MORE THAN ONE FILE?  Y/(N):n
PROCESSING COMPLETED FOR L13
L14           17 DUPLICATE REMOVE L13 (5 DUPLICATES REMOVED)

=> d 1-17 bib ab

L14  ANSWER 1 OF 17     MEDLINE on STN
Full Text
AN   1998032608     MEDLINE
DN   PubMed ID: 9365904
TI   Cation permeability of a cloned rat epithelial amiloride-sensitive Na+
     channel.
AU   Ismailov I I; Shlyonsky V G; Alvarez O; Benos D J
CS   Department of Physiology and Biophysics, University of Alabama at
     Birmingham 35294-0005, USA.. Ismailov@PhyBio.bhs.uab.Edu
NC   DK 37206 (NIDDK)
SO   Journal of physiology, (1997 Oct 15) 504 ( Pt 2) 287-300.
     Journal code: 0266262. ISSN: 0022-3751.
```

CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199801
ED Entered STN: 19980129
Last Updated on STN: 19980129
Entered Medline: 19980113
AB 1. Conductance of heterotrimeric rat epithelial Na+ channels (alpha, beta, gamma-rENaCs) for Li+ and Na+ in planar lipid bilayers was a non-linear function of ion concentration, with a maximum of 30.4 +/- 2.9 pS and 18.5 +/- 1.9 pS at 1 M Li+ and Na+, respectively. 2. The alpha, beta, gamma-rENaC conductance measured in symmetrical mixtures of Na(+)-Li+ (1 M) exhibited an anomalous mole fraction dependence, with a minimum at 4:1 Li+ to Na+ molar ratio. 3. Permeability ratios PK/PNa and PLi/PNa of the channel calculated from the bionic reversal potentials were dependent on ion concentration: PK/PNa was 0.11 +/- 0.01, and PLi/PNa was 1.6 +/- 0.3 at 50 mM; PK/PNa was 0.04 +/- 0.01 and PLi/PNa was 2.5 +/- 0.4 at 3 M, but differed from the ratios of single-channel conductances in symmetrical Li+, Na+ or K+ solutions. The permeability sequence determined by either method was Li+ > Na+ > K+ >> Rb+ Cs+. 4. **Predictions** of a **model** featuring **two** binding **sites** and three energy barriers (2S3B), and allowing double occupancy, developed on the basis of single ion current-voltage relationships, are in agreement with the observed conductance maximum in single ion experiments, conductance minimum in the mole fraction experiments, non-linearity of the current-voltage curves in bionic experiments, and the concentration dependence of permeability ratios. 5. Computer simulations using the 2S3B **model** recreate the ion concentration dependencies of single-channel conductance observed for the immunopurified bovine renal amiloride-sensitive Na+ channel, and short-circuit current in frog skin, thus supporting the hypothesis that ENaCs form a core conduction unit of epithelial Na+ channels.

L14 ANSWER 2 OF 17 MEDLINE on STN DUPLICATE 1
Full Text
AN 97227085 MEDLINE
DN PubMed ID: 9131945
TI Cytochromes P450 mediating the N-demethylation of amitriptyline.
AU Ghahramani P; Ellis S W; Lennard M S; Ramsay L E; Tucker G T
CS Department of Medicine and Pharmacology, University of Sheffield, Royal Hallamshire Hospital, UK.
SO British journal of clinical pharmacology, **(1997 Feb)** 43 (2) 137-44.
Journal code: 7503323. ISSN: 0306-5251.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199704
ED Entered STN: 19970507
Last Updated on STN: 19970507
Entered Medline: 19970430
AB AIMS: Using human liver microsomes and heterologously expressed human enzymes, we have investigated the involvement of CYPs 1A2, 2C9, 2C19, 2D6 and 3A4 in the N-demethylation of amitriptyline (AMI), with a view to defining likely influences on its clinical **pharmacokinetics**. METHODS: The kinetics of formation of nortriptyline (NT) from AMI were measured over the substrate concentration range 1-500 microM, using liver microsomes from four extensive metabolisers (EM) and one poor metaboliser (PM) with respect to CYP2D6 activity. RESULTS: The data were best

described by a **two-site model** comprising a Michaelis-Menten function for a high affinity site and a Hill function for a low affinity site. The activity at the low affinity site was eliminated by triacetyloleandomycin and ketoconazole, selective inhibitors of CYP3A4, such that the kinetics were then described by a **two-site model** comprising **two** Michaelis-Menten functions. A further decrease in activity was associated with the addition of the CYP2C9 inhibitor sulphaphenazole such that the residual kinetics were best described by a single Michaelis-Menten function. The addition of quinidine, a selective inhibitor of CYP2D6, along with triacetyloleandomycin and sulphaphenazole produced an additional decrease in the rate of NT formation in all but the PM liver, but did not completely eliminate the reaction. The remaining activity was best described by a single Michaelis-Menten function. Inhibitors of CYP1A2 (furafylline) and CYP2C19 (mephenytoin) did not impair NT formation. Microsomes from yeast cells expressing CYP2D6 and from human lymphoblastoid cells expressing CYP3A4 or CYP2C9-Arg N-demethylated AMI, but those from cells expressing CYPs 1A2 and 2C19 did not. CONCLUSIONS: We conclude that CYPs 3A4, 2C9 and 2D6 together with an unidentified enzyme, but not CYPs 1A2 and 2C19, mediate the N-demethylation of AMI. Thus, the clinical **pharmacokinetics** of AMI would be expected to depend upon the net activities of all of these enzymes. However, the quantitative importance of each isoform is difficult to **predict** without knowledge of the exposure of the enzymes in vivo to AMI.

L14 ANSWER 3 OF 17 MEDLINE on STN
Full Text
AN 97475426 MEDLINE
DN PubMed ID: 9334938
TI In vivo saturation kinetics of two dopamine transporter probes measured using a small animal positron emission tomography scanner.
AU Hume S P; Brown D J; Ashworth S; Hirani E; Luthra S K; Lammertsma A A
CS PET Methodology Group, Hammersmith Hospital, London, UK.
SO Journal of neuroscience methods, **(1997 Sep 5)** 76 (1) 45-51.
Journal code: 7905558. ISSN: 0165-0270.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199711
ED Entered STN: 19980109
Last Updated on STN: 19980109
Entered Medline: 19971126
AB When estimated in vitro, the parameters which describe the binding of radiolabelled analogues of cocaine to sites on the dopamine transporter are very much influenced by the methodology used. In the present study, a small animal positron emission tomography (PET) scanner was used to estimate in vivo saturation kinetics for two carbon-11 labelled compounds presently used to monitor dopamine terminal function. The binding of [11C]CFT (WIN 35,428) in rat striatum was adequately described by a single-site **model**, giving an apparent dissociation constant corresponding to an intravenous dose of 242 nmol/kg. In contrast, the binding of [11C]RTI-121 was better described by a **two-site model** with the 'high-affinity' site or state (dissociation constant = 1 nmol/kg) being significantly occupied at doses routinely used in PET scanning. Such findings cannot readily be **predicted** from in vitro work, but could aid in both the choice of ligand and the **model** used in quantification of scan data. While multi-dose in vivo PET studies are difficult in man, rat PET can easily be employed either pre-clinically for putative radioligands, or experimentally, to study drug interactions and receptor occupancy related to functional efficacy.

L14 ANSWER 4 OF 17 MEDLINE on STN DUPLICATE 2
Full Text
AN 1999080608 MEDLINE
DN PubMed ID: 9863240
TI **Two-site** absorption **model** fits to pharmacokinetic data of gemfibrozil in man.
AU Liu X D; Xie L; Wang J; Zhou Y S; Wang Z; Liu G Q
CS Center of Drug Metabolism and Pharmacokinetics, China Pharmaceutical University, Nanjing.
SO Yao xue xue bao = Acta pharmaceutica Sinica, **(1996)** 31 (10) 737-41.
Journal code: 21710340R. ISSN: 0513-4870.
CY China
DT Journal; Article; (JOURNAL ARTICLE)
LA Chinese
FS Priority Journals
EM 199902
ED Entered STN: 19990301
Last Updated on STN: 19990301
Entered Medline: 19990218
AB The plasma concentration-time data of gemfibrozil in 8 male subjects were determined after an oral dose of 600 mg. Two-peak concentrations in plasma were observed. A kind of one-compartment **model** with **two-sites** of drug absorption was proposed and used to fit these data. A good agreement between observed and **predicted** data was found in all subjects with correlation indexes (gamma 2) > 0.99. The corresponding pharmacokinetic parameters were estimated as follows: Tmax1, 1.10 +/- 0.46 h; Tmax2, 2.60 +/- 0.73 h; Cmax1, 13.62 +/- 4.30 micrograms.ml-1; Cmax2, 17.22 +/- 3.83 micrograms.ml-1; T1, 0.06 +/- 0.06 h; T2, 1.42 +/- 0.57 h and T3, 1.79 +/- 0.60 h.

L14 ANSWER 5 OF 17 MEDLINE on STN DUPLICATE 3
Full Text
AN 96263347 MEDLINE
DN PubMed ID: 8786978
TI Regional drug delivery II: relationship between drug targeting index and pharmacokinetic parameters for three non-steroidal anti-inflammatory drugs using the rat air pouch **model** of inflammation.
AU Stevens A J; Martin S W; Brennan B S; McLachlan A; Gifford L A; Rowland M; Houston J B
CS Department of Pharmacy, University of Manchester, United Kingdom.
SO Pharmaceutical research, **(1995 Dec)** 12 (12) 1987-96.
Journal code: 8406521. ISSN: 0724-8741.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199609
ED Entered STN: 19961008
Last Updated on STN: 19961008
Entered Medline: 19960926
AB PURPOSE: To quantify the advantage gained by direct administration to a target **site** for **two** non-steroidal anti-inflammatory drugs (NSAIDs) piroxicam and diclofenac in the rat air pouch **model** of inflammation. To derive a **model** relating drug targeting index (DTI) to the pharmacokinetic parameters of the target and systemic sites, and to compare **predictions** with observations. METHODS: DTI was calculated based on area under the concentration time curve at target (pouch) and systemic site (venous blood) following administration into and sampling from both sites. A **model** was derived relating DTI to systemic

clearance, target permeability, plasma protein binding and fraction of the targeted dose that is systemically available. RESULTS: Both NSAIDs exhibited linear **pharmacokinetics** over the dose ranges studies. They differed primarily in total body clearance which was approximately 16 fold greater for diclofenac (213 ml hr-1 per 250 g) than piroxicam (13 ml hr-1 per 250 g). Observed DTIs (11, 114 and 276 for piroxicam, S[+]ibuprofen [studied previously] and diclofenac) were ranked in order of total body clearance but were approximately 7.5 fold lower than **predicted** (101, 700 and 2214 respectively). CONCLUSIONS: The discrepancy was explained by the influx of the plasma binding protein, albumin, into the target site due to increased vascular permeability associated with the inflammatory response. The originally derived equation for DTI, which assumed only unbound drug diffuses across the target site, was modified to take into account the simultaneous flux of bound drug.

L14 ANSWER 6 OF 17 MEDLINE on STN
Full Text
AN 95363693 MEDLINE
DN PubMed ID: 7636740
TI **Prediction** of in vivo disposition from in vitro systems: clearance of phenytoin and tolbutamide using rat hepatic microsomal and hepatocyte data.
AU Ashforth E I; Carlile D J; Chenery R; Houston J B
CS Department of Pharmacy, University of Manchester, U.K.
SO Journal of pharmacology and experimental therapeutics, **(1995 Aug)** 274 (2) 761-6.
Journal code: 0376362. ISSN: 0022-3565.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199509
ED Entered STN: 19950921
Last Updated on STN: 19950921
Entered Medline: 19950908
AB The kinetics of oxidation of phenytoin and tolbutamide were determined in freshly isolated hepatocytes and hepatic microsomes from male Sprague-Dawley rats. Similar enzyme kinetic **models** are applicable to the data from both in vitro systems; a **two-site model** for phenytoin with a high affinity (Km = 1-5 microM, based on unbound drug concentration), low capacity site and a low affinity, high capacity site, and a one-site **model** for tolbutamide. Steady-state infusion studies were performed to characterize the Michaelis-Menten parameters for phenytoin disposition in vivo, these data could also be described by a **two-site** metabolism **model** (Km 1.3 microM, intrinsic clearance 62 ml/min for unbound drug for the high affinity site). Comparison of in vivo and in vitro parameters (after scaling the latter parameters for either hepatocyte yield or microsomal recovery) showed excellent **prediction** of in vivo clearance of unbound drug from hepatocyte data (55 ml/min) but underprediction from microsomal data (17 ml/min). In contrast to phenytoin, the in vivo clearance of tolbutamide (1.5 ml/min for unbound drug) was equally well **predicted** by both hepatocyte (2.4 ml/min) and microsomal (3.1 ml/min) studies. The difference between the utility of in vitro systems to **predict** the in vivo clearance of these two drugs, which show similar pharmacrokinetic properties (low clearance restricted to unbound drug concentration in blood), may be a consequence of the particular terminal metabolite formed in each in vitro system.(ABSTRACT TRUNCATED AT 250 WORDS)

L14 ANSWER 7 OF 17 MEDLINE on STN

Full Text
AN 95279961 MEDLINE
DN PubMed ID: 7760017
TI Rapid inactivation of depletion-activated calcium current (ICRAC) due to local calcium feedback.
AU Zweifach A; Lewis R S
CS Department of Molecular and Cellular Physiology, Stanford University School of Medicine, California 94305, USA.
NC AI08568 (NIAID)
GM47354 (NIGMS)
SO Journal of general physiology, **(1995 Feb)** 105 (2) 209-26.
Journal code: 2985110R. ISSN: 0022-1295.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199506
ED Entered STN: 19950707
Last Updated on STN: 19980206
Entered Medline: 19950627
AB Rapid inactivation of Ca2+ release-activated Ca2+ (CRAC) channels was studied in Jurkat leukemic T lymphocytes using whole-cell patch clamp recording and [Ca2+]i measurement techniques. In the presence of 22 mM extracellular Ca2+, the Ca2+ current declined with a biexponential time course (time constants of 8-30 ms and 50-150 ms) during hyperpolarizing pulses to potentials more negative than -40 mV. Several lines of evidence suggest that the fast inactivation process is Ca2+ but not voltage dependent. First, the speed and extent of inactivation are enhanced by conditions that increase the rate of Ca2+ entry through open channels. Second, inactivation is substantially reduced when Ba2+ is present as the charge carrier. Third, inactivation is slowed by intracellular dialysis with BAPTA (12 mM), a rapid Ca2+ buffer, but not by raising the cytoplasmic concentration of EGTA, a slower chelator, from 1.2 to 12 mM. Recovery from fast inactivation is complete within 200 ms after repolarization to -12 mV. Rapid inactivation is unaffected by changes in the number of open CRAC channels or global [Ca2+]i. These results demonstrate that rapid inactivation of ICRAC results from the action of Ca2+ in close proximity to the intracellular mouths of individual channels, and that Ca2+ entry through one CRAC channel does not affect neighboring channels. A simple **model** for Ca2+ diffusion in the presence of a mobile buffer **predicts multiple** Ca2+ inactivation **sites** situated 3-4 nm from the intracellular mouth of the pore, consistent with a location on the CRAC channel itself.

L14 ANSWER 8 OF 17 MEDLINE on STN
Full Text
AN 95182057 MEDLINE
DN PubMed ID: 7876790
TI Vitreous humor cocaine and metabolite concentrations: do postmortem specimens reflect blood levels at the time of death?.
AU McKinney P E; Phillips S; Gomez H F; Brent J; MacIntyre M; Watson W A
CS Rocky Mountain Poison and Drug Center, Denver General Hospital, University of Colorado Health Sciences Center.
SO Journal of forensic sciences, **(1995 Jan)** 40 (1) 102-7.
Journal code: 0375370. ISSN: 0022-1198.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199504

ED Entered STN: 19950419
Last Updated on STN: 19950419
Entered Medline: 19950404

AB The interpretation of postmortem cocaine concentrations is made in an attempt to estimate drug concentrations present at the time of death and thus infer not only drug presence but drug toxicity. Previous data suggest that changes in postmortem blood cocaine concentrations over time are not **predictable** and interpretation of cocaine levels should be done with caution. However, these data come from autopsy case series where vital information, such as blood cocaine concentration at the time of death, dose and time since last use, and postmortem interval is often not known. The purpose of this study was to characterize postmortem changes in cocaine and metabolite concentrations relative to premortem concentrations over time at **two** anatomic **sites**: peripheral blood and vitreous humor, in a controlled, large animal **model**. Juvenile swine were given cocaine HCl 10 mg/kg as an IV bolus which resulted in seizures and wide complex tachycardia. Five minutes after cocaine administration, animals were euthanized. At time of death and eight hours postmortem, femoral venous blood and vitreous humor (VH) samples were obtained for quantitation of cocaine, benzoyl ecgonine (BE), and ecgonine methyl ester (EME) by GC/MS. There were no significant increases over time in mean femoral vein concentrations of cocaine or BE. However, a large interanimal variability in direction and magnitude of concentration changes was seen. Mean EME concentrations at the femoral site increased significantly over 8 hours ($P < 0.03$). Mean VH cocaine concentrations at time of death were significantly lower than corresponding blood concentrations ($P < 0.02$).(ABSTRACT TRUNCATED AT 250 WORDS)

L14 ANSWER 9 OF 17 MEDLINE on STN
Full Text

AN 94157581 MEDLINE
DN PubMed ID: 8113817
TI Methyl 3 beta-(4-[125I]iodophenyl)tropane-2 beta-carboxylate in vitro binding to dopamine and serotonin transporters under "physiological" conditions.
AU Laruelle M; Giddings S S; Zea-Ponce Y; Charney D S; Neumeyer J L; Baldwin R M; Innis R B
CS Department of Psychiatry, Yale University School of Medicine, West Haven, Connecticut.
NC NIMH R43-MH48243 (NIMH)
SO Journal of neurochemistry, **(1994 Mar)** 62 (3) 978-86.
Journal code: 2985190R. ISSN: 0022-3042.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199403
ED Entered STN: 19940406
Last Updated on STN: 19950206
Entered Medline: 19940328

AB Methyl 3 beta-(4-[125I]iodophenyl)tropane-2 beta-carboxylate ([123I]beta-CIT) is a single photon emission computed tomographic radiotracer for in vivo labeling of dopamine (DA) and serotonin (5-HT) transporters. Single photon emission computed tomographic experiments in nonhuman primates showed that [123I]beta-CIT in vivo binding to DA transporters had a much slower washout than binding to 5-HT transporters. This observation was not **predicted** from previously published in vitro studies. These studies, performed at 22 degrees C in nonphysiological buffer, reported similar affinity of [125I]beta-CIT for DA and 5-HT transporters. We now report [125I]beta-CIT binding parameters to fresh

rat membranes at 22 degrees C and 37 degrees C, in a buffer mimicking the composition of cerebrospinal fluid. At both temperatures, binding to DA transporters was best fit by a **two-site model**, whereas binding to 5-HT transporters was compatible with one population of sites. At 22 degrees C, [125I]beta-CIT showed similar affinity to high-affinity DA (0.39 nM) and 5-HT transporter sites (0.47 nM). Increasing the incubation temperature from 22 degrees C to 37 degrees C reduced binding to DA transporters by 60%, whereas binding to 5-HT transporters was only marginally affected. In vitro kinetic experiments failed to detect significant differences in on or off rates that could explain the observed in vivo kinetics. These experiments thus failed to explain [125I]beta-CIT in vivo uptake kinetics, suggesting the existence of specific factors affecting the in vivo situation.

L14 ANSWER 10 OF 17 MEDLINE on STN
Full Text
AN 94180329 MEDLINE
DN PubMed ID: 8133462
TI Pharmacokinetic modeling of the sinusoidal efflux of anionic ligands from the isolated perfused rat liver: the influence of albumin.
AU Proost J H; Nijssen H M; Strating C B; Meijer D K; Groothuis G M
CS Department of Pharmacology and Therapeutics, University Centre for Pharmacy, University of Groningen, The Netherlands.
SO Journal of pharmacokinetics and biopharmaceutics, **(1993 Aug)** 21 (4) 375-94.
Journal code: 0357115. ISSN: 0090-466X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199404
ED Entered STN: 19940428
Last Updated on STN: 19980206
Entered Medline: 19940420
AB This study contains a pharmacokinetic analysis on the efflux of organic anions from the liver into the bloodstream (sinusoidal efflux) with specific reference to the influence of albumin. The net sinusoidal efflux rate of dibromosulfophthalein (DBSP) from preloaded livers, being the resultant of sinusoidal efflux and reuptake of ligand by hepatocytes downstream the sinusoid, can be strongly increased by the presence of bovine serum albumin (BSA), a protein having **multiple** binding **sites** for DBSP. We previously attributed this effect to a reduction of reuptake through extracellular binding of the organic anion to the protein, rather than to an intrinsic stimulatory effect on the actual membrane transport process from the cells. In the present study we tested this hypothesis using a pharmacokinetic multicompartment liver **model**. This **model** resembles the parallel tube **model** in that the liver is described by several compartments placed in series instead of a single well-stirred compartment and it takes into account rates of dissociation and association in binding to proteins in the sinusoidal space. The **model** parameters were fitted from the sinusoidal efflux and biliary excretion data from efflux experiments measuring the stimulatory effect of various concentrations of BSA. Equilibrium binding of DBSP to albumin as well as the dissociation rate constant (koff) were determined in vitro with rapid filtration techniques. The experimental data could not be fitted satisfactorily when using the experimentally obtained values of the protein association and dissociation rate constants (kon and koff). However, they could be simulated accurately assuming 16 times higher values for the association and dissociation rate constant compared to those determined in vitro. Time constants of the perfusate flow, liver

(re)uptake, and protein association and dissociation indicate that binding equilibrium does not exist within the sinusoids and that, in particular at low protein concentrations, the net sinusoidal efflux rate is association rate-limited: A large fraction of the ligand effluxed from the cell into the median is taken up by the hepatocyte before binding to the proteins occurs. Higher kon and koff values **predicted** by the **model** might indicate altered DBSP-albumin binding characteristics upon passage through the liver but alternatively can be explained by an intrinsic effect of albumin on the carrier-mediated efflux process. Efflux experiments showed a marked stimulatory effect of the protein on sinusoidal efflux but only a moderate effect on biliary excretion, despite a strong decrease in liver content. These patterns indicate that sinusoidal efflux and biliary excretion occur from two different intracellular compartments that equilibrate slowly.

L14 ANSWER 11 OF 17 MEDLINE on STN DUPLICATE 4
Full Text
AN 92206826 MEDLINE
DN PubMed ID: 1803996
TI Characteristics of ceftriaxone binding to immunoglobulin G and potential clinical significance.
AU Sun H; Chow M S; Maderazo E G
CS Department of Medicine, Hartford Hospital, Connecticut 06115.
SO Antimicrobial agents and chemotherapy, **(1991 Nov)** 35 (11) 2232-7.
Journal code: 0315061. ISSN: 0066-4804.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199204
ED Entered STN: 19920509
Last Updated on STN: 19920509
Entered Medline: 19920424
AB The interaction between immunoglobulin G (IgG) and ceftriaxone was studied. Using an ultrafiltration method, we performed dose ranging studies at a ceftriaxone concentration range of 1 to 720 micrograms/ml in the presence of various concentrations of human IgG, human serum albumin (HSA), and combinations of IgG and HSA at pH 7.4 and 37 degrees C. The results showed that ceftriaxone binding to IgG was nonlinear and was consistent with the presence of **two** binding **sites** that possess different binding capacities and affinities. Except for increased peak percent binding as the IgG concentration increased, the binding characteristics did not change with IgG concentration. Binding to HSA was consistent, with the presence of only one high-affinity binding site. A mathematical **model** based on the observed data was constructed; this **model** was used to **predict** protein binding at various concentrations of drug, IgG, HSA, or combinations of IgG and HSA in buffer and in plasma medium. Correlations between the observed versus the **predicted** values were excellent in both media. Simulations with the **model** indicated that patients with hypergammaglobulinemia have an increased potential of being exposed to prolonged subinhibitory concentrations of ceftriaxone if the drug is given once every 24 h.

L14 ANSWER 12 OF 17 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
Full Text
AN 1992:69488 BIOSIS
DN PREV199293037943; BA93:37943
TI CORRELATION OF IN-VITRO PARAMETERS OF ANTIMICROBIAL ACTIVITY WITH PROPHYLACTIC EFFICACY IN AN INTRADERMAL **MODEL** OF STAPHYLOCOCCUS-AUREUS INFECTION.

AU WARREN M D [Reprint author]; KERNODLE D S; KAISER A B
CS DIV INFECT DIS, DEP MED, VANDERBILT UNIV SCH MED, NASHVILLE, TENN 37232, USA
SO Journal of Antimicrobial Chemotherapy, (1991) Vol. 28, No. 5, pp. 731-740. CODEN: JACHDX. ISSN: 0305-7453.
DT Article
FS BA
LA ENGLISH
ED Entered STN: 2 Feb 1992
Last Updated on STN: 2 Feb 1992
AB Cephalosporins differ in their ability to prevent staphylococcal wound infection. Although the reasons for the observed differences are not fully understood, the susceptibility of cephalosporins to hydrolysis by staphylococcal β-lactamase has been correlated with failures of prophylaxis. To investigate the effect of β-lactamase stability and other in-vitro parameters of the bacterial-antimicrobial interaction on the efficacy of antimicrobial prophylaxis, two β-lactamase-stable agents, cefuroxime and cefmetazole were compared to cefazolin and cefamandole in an in-vivo **model** of intradermal infection employing four strains of Staphylococcus aureus. Following intraperitoneal administration of a single dose of cephalosporin or placebo, guinea pigs were inoculated at **multiple** intradermal **sites** with 2 ×107 cfu of a strain of staphylococcus. For three strains, the area of induration at 24 h following inoculation was significantly smaller in guinea pigs receiving prophylaxis with cephalosporins versus placebo; no cephalosporin was effective against the fourth strain. Differences were also noted among the cephalosporins; prophylaxis with cefuroxime and cefmetazole resulted in smaller lesions than seen in animals given cefazolin or cefamandole. Poor correlation was noted between results of the in-vivo **model** and in-vitro determinants of the bacterial-antimicrobial interaction which were MIC values, time-kill curves, and the rates of β-lactamase-mediated cephalosporin hydrolysis by the different strains. The **model** demonstrated unexplained failures of prophylaxis and unexpected differences in efficacy of various cephalosporins as has been described before. This study highlights the need for an improved animal **model** of surgical antimicrobial prophylaxis and the identification of in-vitro determinants that **predict** in-vivo prophylactic efficacy more accurately.

L14 ANSWER 13 OF 17 MEDLINE on STN
Full Text
AN 90310932 MEDLINE
DN PubMed ID: 2114617
TI Nonlinear binding of valproic acid (VPA) and E-delta 2-valproic acid to rat plasma proteins.
AU Semmes R L; Shen D D
CS Department of Pharmaceutics, School of Pharmacy, University of Washington, Seattle 98195.
NC NS-22662 (NINDS)
SO Pharmaceutical research, **(1990 May)** 7 (5) 461-7.
Journal code: 8406521. ISSN: 0724-8741.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199008
ED Entered STN: 19900921
Last Updated on STN: 19900921
Entered Medline: 19900816

AB The binding characteristics of valproic acid (VPA) and its pharmacologically active monounsaturated metabolite, E-delta 2-VPA, to rat plasma proteins were compared. The plasma free fraction was determined by a rapid equilibrium procedure, which minimizes the interfering effects of nonesterified fatty acids liberated by in vitro lipolysis. Nonlinear binding behavior was observed with both compounds over their respective pharmacologic concentration range. **Multiple** binding-**site models** were invoked to explain the binding isotherm. The 2-unsaturated compound has a much higher affinity for the rat plasma proteins (mainly albumin) than its saturated precursor. The equilibrium association constants for the high- and intermediate-affinity sites were more than an order of magnitude higher with E-delta 2-VPA than with VPA (10(4)-10(6) versus 10(3) M-1). This difference in binding affinity was also reflected by a lower plasma free fraction for E-delta 2-VPA compared with VPA (much less than 10 versus greater than 20% at total concentrations of less than 100 micrograms/ml). A more pronounced dose- and concentration-dependent variation in the distribution and clearance kinetics is **predicted** for the 2-unsaturated analogue compared to VPA. Also, the structural dependency in plasma protein binding observed with these branched-chain fatty acids may provide insights into the mechanism of interaction between fatty acyl molecules and albumin.

L14 ANSWER 14 OF 17 MEDLINE on STN
Full Text
AN 90252214 MEDLINE
DN PubMed ID: 2160135
TI A physiological pharmacokinetic description of the tissue distribution and enzyme-inducing properties of 2,3,7,8-tetrachlorodibenzo-p-dioxin in the rat.
AU Leung H W; Paustenbach D J; Murray F J; Andersen M E
CS Syntex Corporation, Palo Alto, California 94304.
SO Toxicology and applied pharmacology, **(1990 May)** 103 (3) 399-410.
Journal code: 0416575. ISSN: 0041-008X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199006
ED Entered STN: 19900720
Last Updated on STN: 19970203
Entered Medline: 19900618
AB A five-compartment physiologically based pharmacokinetic (PB-PK) **model** was developed to describe the tissue disposition of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in the Sprague-Dawley rat. This description included blood, liver, fat, muscle/skin, and visceral tissue groups. On the basis of other literature, the liver compartment was modeled to include **two** TCDD-binding **sites**, corresponding to a cytosolic receptor and a microsomal binding protein. A pharmacodynamic description was developed in which microsomal enzyme induction, both of arylhydrocarbon hydroxylase activity and of the amount of the microsomal TCDD-binding protein, was linked to fractional occupancy of the cytosolic receptor. This description was then used to analyze previously published data on TCDD disposition. The dissociation constant of the cytosolic Ah receptor (KB1) in vivo was estimated to be 15 pM by fitting enzyme induction data from McConnell et al. (1984). The ratio of liver to fat concentration of TCDD (about 4:1) was found to be primarily determined by the dissociation constant of the microsomal binding protein (7 nM) and the basal and induced concentration of this protein in the liver (25 and 200 nmol/liver, respectively). With these parameter values, the tissue distribution of TCDD in fat and liver, the **two** primary **sites** of

accumulation, was accurately described following either single or repeated dosing with TCDD in the rat. The pharmacokinetic behavior described by the **model** was extremely sensitive to binding affinities, and only moderately sensitive to binding capacities in the dose range studied. Induction of microsomal TCDD-binding proteins was necessary in order to account for the differences in disposition at low (0.01 microgram/kg) and high (1.0 microgram/kg) daily doses of TCDD. Since the tumorigenicity of TCDD in rats is believed to be correlated with the biological responses of the Ah-TCDD complex, the present physiological pharmacokinetic description, which contains information on receptor occupancy at various dose levels, provides a plausible mechanistic connection for devising pharmacodynamic **models** which **predict** the cancer risk of TCDD in the rat.

L14 ANSWER 15 OF 17 MEDLINE on STN DUPLICATE 5
Full Text
AN 88062059 MEDLINE
DN PubMed ID: 3681664
TI Physiologically based pharmacokinetic **model** for the renal clearance of phenolsulfonphthalein and the interaction with probenecid and salicyluric acid in the dog.
AU Russel F G; Wouterse A C; van Ginneken C A
CS Department of Pharmacology, University of Nijmegen, The Netherlands.
SO Journal of pharmacokinetics and biopharmaceutics, **(1987 Aug)** 15 (4) 349-68.
Journal code: 0357115. ISSN: 0090-466X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198801
ED Entered STN: 19900305
Last Updated on STN: 19900305
Entered Medline: 19880111
AB Plasma kinetics and renal excretion of intravenous phenolsulfonphthalein (PSP, 1.0 g), with and without concomitant administration of probenecid or salicyluric acid (SUA), were studied in the Beagle dog. Pharmacokinetic analysis revealed that tubular secretion is the predominant route of excretion, and that secretion is inhibited by probenecid and SUA. A physiologically based kidney **model** was developed that incorporates the functional characteristics of the kidney that determine the excretion of PSP, i.e., renal plasma flow, urine flow, nonlinear protein binding, glomerular filtration, tubular secretion, and tubular accumulation. The **model** enabled an accurate description and analysis of the measured plasma levels and renal excretion rates. The interaction with probenecid and SUA could be adequately described with the **model** by inhibition of the carrier-mediated uptake of PSP into the proximal tubular cells. However, both compounds clearly differed in their inhibitory action. Whereas probenecid showed simple competitive inhibition, for SUA a considerably more complex interaction (**two-site** competitive system) had to be taken into consideration. Especially in the interaction experiments, only satisfactory fits to the **model** were obtained when secretion was assumed to be dependent on unbound PSP concentrations. **Model** calculations showed that in the control experiments tubular secretion was accompanied by a pronounced accumulation of PSP within the proximal tubular cells, which was clearly diminished in presence of probenecid or SUA. The **predicted** accumulation ratios were in good agreement with previous studies.

L14 ANSWER 16 OF 17 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
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AN 1986:145907 BIOSIS
DN PREV198681056323; BA81:56323
TI INTERACTIONS OF AMILORIDE AND OTHER BLOCKING CATIONS WITH THE APICAL SODIUM CHANNEL IN THE TOAD URINARY BLADDER.
AU PALMER L G [Reprint author]
CS DEP OF PHYSIOL, CORNELL UNIV MED COLL, NEW YORK, NY 10021, USA
SO Journal of Membrane Biology, (1985) Vol. 87, No. 3, pp. 191-200.
CODEN: JMBBBO. ISSN: 0022-2631.
DT Article
FS BA
LA ENGLISH
ED Entered STN: 25 Apr 1986
Last Updated on STN: 25 Apr 1986
AB A simple **model** of the action of amiloride to block apical Na channels in the toad urinary bladder was tested. According to the **model**, the positively charged form of the drug binds to a site in the lumen of the channel within the electric field of the membrane. In agreement with the **predictions** of the **model**: (1) The voltage dependence of amiloride block was consistent with the assumption of a single amiloride binding site, at which about 15% of the transmembrane voltage is sensed, over a voltage range of ±160 mV. (2) The time course of the development of voltage dependence was consistent with that **predicted** from the rate constants for amiloride binding previously determined. (3) The ability of organic cations to mimic the action of amiloride showed a size dependence implying a restriction of access to the binding site, with an effective diameter of about 5 angstroms. In a fourth test, divalent cations (Ca, Mg, Ba and Sr) were found to block Na channels with a complex voltage dependence, suggesting that these ions interact with **two** or more **sites**, at least one of which may be within the lumen of the pore.

L14 ANSWER 17 OF 17 MEDLINE on STN
Full Text
AN 80117351 MEDLINE
DN PubMed ID: 529019
TI Multiple receptor responses: a new concept to describe the relationship between pharmacological effects and **pharmacokinetics** of a drug: studies on clonidine in the rat and cat.
AU Paalzow L K; Edlund P O
SO Journal of pharmacokinetics and biopharmaceutics, **(1979 Oct)** 7 (5) 495-510.
Journal code: 0357115. ISSN: 0090-466X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198004
ED Entered STN: 19900315
Last Updated on STN: 19980206
Entered Medline: 19800426
AB The time course of an observed pharmacological effect is affected not only by the kinetics of the drug levels at the site of action but also by parameters such as the slope and maximum effect of the functional relationship between drug level and response. Using clonidine as a test drug, it was found that the kinetics of its effects on blood pressure and pain responses cannot be described by the time course of clonidine levels in the blood, brain, or the hypothetical tissue compartment of the two-compartment characteristics of this drug. However, the results can be explained assuming that the observed pharmacological effects of a drug are composed of the sum of responses from at least **two** receptor **sites** with different slopes and maximal effects. The effect of intravenously

administered clonidine on blood pressure in the rat was found to be related to the blood concentrations at least at **two** receptor **sites** with opposite effects, one leading to a hypertensive and the other to a hypotensive response. **Predictions** indicate that a maximum decrease of arterial blood pressure is obtained when the steady-state blood concentration of clonidine is about 1 ng/ml and that no effect is seen at 10 ng/ml. Higher levels will produce an increase of the pressure. The kinetics of the analgesic effect of clonidine in the rat could best be related to the brain levels if the observed effect was considered to be derived from the sum of activity at **two** receptor **sites** each producing analgesia. The kinetics of the effects of clonidine on the nictitating membrane of the cat was found to be determined by the kinetics of the drug in the peripheral compartment of the two-compartment open **model**. Consideration of multiple receptor responses is suggested for future studies on the relationship between the kinetics of drug levels and pharmacological responses.

=> log y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	36.42	36.63

STN INTERNATIONAL LOGOFF AT 13:56:40 ON 05 AUG 2004